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*CLINICAL RESEARCH*

# Esophageal mesenchymal tumors: Endoscopy, pathology and immunohistochemistry

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## Abstract

**AIM:** To study the endoscopic, pathological and immunohistochemical features of esophageal mesenchymal tumors.

**METHODS:** Twenty-nine patients diagnosed as esophageal mysenchymal tumors by electronic endoscopy and endoscopic ultrasound (EUS) were observed under light microscopes, and all tissues were stained by the immunohistochemical method. The expression of CD117, CD34, SMA and desmin were measured by staining intensity of cells and positive cell ratios.

**RESULTS:** Endoscopically, esophageal gastrointestinal stromal tumors (GISTs) and leiomyomas (LMs) had similar appearances, showing submucosal protuberant lesions. They all showed low echo images originated from the muscularis propria or muscularis mucosa on EUS. Endoscopy and EUS could not exactly differentiate esophageal GISTs from LMs. Microscopically, there were two kinds of cells: spindle cell type and epitheloid cell type in esophageal GISTs. Leiomyomas and leiomyosarcomas were only of spindle cell type. One malignancy was found in five cases of esophageal GISTs, and one malignancy in 24 cases of leiomyomas and leiomyosarcomas. Using Fisher's exact method, the differences of malignant lesion proportion were not significant between esophageal LMs and GISTs, 1/5 *vs* 1/24 ($P > 0.05$). All cases of esophageal GISTs were positive for CD117, and 3 cases were also positive for CD34. The 24 cases of leiomyomas and leiomyosarcomas were all negative for CD117 and CD34. The differences of positive rates of CD117 and CD34 were significant between esophageal GISTs and LMs, 5/5 *vs* 0/24, 3/5 *vs* 0/24 ($P < 0.005$). All leiomyomas and leiomyosarcomas were positive for SMA, and desmin. Among 5 cases of esophageal GISTs, 2 cases were SMA positive, and 1 case was desmin positive. The differences in positive rates and expression intensity of SMA and desmin were significant between esophageal LMs and GISTs, 24/24 *vs* 2/5, 24/24 *vs* 1/5 ($P < 0.005$).

**CONCLUSION:** The most common esophageal mesenchymal tumors are leiomyomas, and esophageal GISTs are less common. Most of esophageal LMs and GISTs are benign. Endoscopy and EUS are the effective methods to diagnose esophageal mesenchymal tumors and they can provide useful information for the treatment of these tumors. However, they cannot exactly differentiate esophageal GISTs from LMs. Pathological, especially immunohistochemical features are useful to differentiate GISTs from leiomyomas.



**Key words:** Esophageal mesenchymal tumors; Gastrointestinal stromal tumors; Leiomyomas; Endoscopy; Pathology; Immunohistochemistry

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## INTRODUCTION

Traditionally, the gastrointestinal mesenchymal tumors (GIMTs) have been almost uniformly classified as gastrointestinal leiomyomas (LMs). However, recent evidence indicates that most mesenchymal tumors of the gastrointestinal tract are gastrointestinal stromal tumors (GISTs)[1]. It is difficult to differentiate esophageal GISTs from LMs because of their similar appearance. GISTs frequently have malignant potential, therefore, it is important to differentiate GISTs from LMs. GISTs arising in the gastrointestinal tract have been known quite well. Whether there are the same stromal tumors in the esophagus, and whether stromal tumors are the most

frequent mesenchymal tumors of the esophagus, are big concern of clinical doctors[2,3].

## MATERIALS AND METHODS

### Specimen collection

All the patients were in- and outpatients from the First Affiliated Hospital of Nanchang University during June 2004 to November 2005 and they all met with the following two criteria: (1) Endoscopically, the tumors showed submucosal protuberant lesions, and they showed low echo images originated from the muscularis propria or muscularis mucosa on EUS. (2) Microscopically, they were diagnosed as esophageal mesenchymal tumors. All tissue specimens were obtained by the following 3 methods: biopsy, endoscopic mucosal resection (EMR) or surgical operation.

### Methods

All tissue specimens were fixed in 10% formalin and processed routinely for paraffin embedding. Sections of 4-mm thick were stained with hematoxylin and eosin, and observed by light microscopy. Then all cases were stained for CD117, CD34, SMA, and desmin. All antibodies were purchased from Beijing Zhongshan Corporation. The detailed procedures were carried out according to instructions of the kits.

### Criteria for histopathology

First, esophageal mesenchymal tumors: According to the criteria of 2005 WHO Oncopathology and Genetics[4], if spindle cells and epitheloid cells were shown microscopically, esophageal mesenchymal tumors can be diagnosed. Sencond, criteria for assessing malignancy of gastrointestinal stromal tumors: according to the criteria of 2005 WHO Oncopathology and Genetics and the advice of Singer and Miettinen[4-6], GISTs were diagnosed as malignant when the following criteria were met: tumor size $\geqslant$ 5 cm, nuclear mitotic figure > 5/50 HPF. GISTs were diagnosed as benign: tumor size < 5 cm, nuclear mitotic figure < 5/50 HPF. GISTs were diagnosed as potentially malignant: tumor size $\geqslant$ 5 cm, nuclear mitotic figure < 5/50 HPF or tumor size < 5 cm, nuclear mitotic figure > 5/50 HPF. At the same time, tumor hemorrhage/necrosis, peripheral invasive growth, lymph node metastasis and metastasis to another organ are all considered also. Third, criteria for leiomyosarcomas: according to the criteria of 2005 WHO Oncopathology and Genetics and internal reports[4,7,8], tumor size $\geqslant$ 5 cm, nuclear mitotic figure > 5/50 HPF, tumor hemorrhage/necrosis, peripheral invasive growth and metastasis.

### Assessment for immunohistochemical results

Positive results were indicated if the cytoplasm was stained brown, and cell membrane was stained positive for CD34 and CD117. The categories were (+): more than 10% of cells stained; (-): less than 10% of cells stained. Positive control: CD117, an indicator of the known GISTs; CD34, an indicator of vascular endothelial cells in tumors; SMA, an indicator of normal smooth muscles in vascular walls or esophageal walls; Desmin, an indicator of normal smooth muscles in esophageal walls. Negative control: the primary antibody was replaced by PBS for negative control.

**Table 1 Clinical findings of 29 cases of esophageal mesenchymal tumors**

| Tumor type | *n* | Dysphagia | Heart burn/ retrosternal pain | Hemorrhage | Stomachache | Asymptomatic |
|---|---|---|---|---|---|---|
| LMs | 24 | 4 | 7 | 1 | 2 | 10 |
| GISTs | 5 | 1 | 1 | 1 | 0 | 2 |
| Total | 29 | 5 | 8 | 2 | 2 | 12 |

Tested by Fisher's exact method, the differences of symptoms are not significant between esophageal LMs and GISTs ($P > 0.05$).

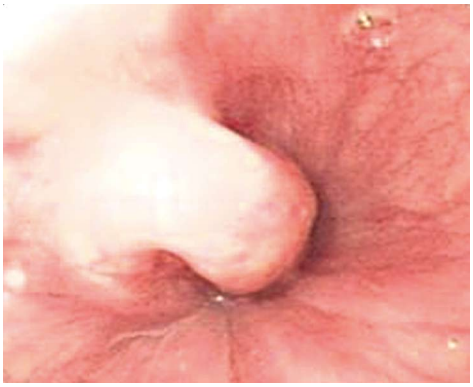

**Figure 1** Endoscopic image of esophageal stromal tumors.

### Statistical analysis

Data was tested using Fisher's exact method. A $P$ value less than 0.05 was considered statistically significant.

## RESULTS

### Clinical data

Among 29 cases of esophageal mesenchymal tumors diagnosed by endoscopy, pathology and immunohistochemistry, 5 cases were esophageal GISTs, 23 cases were leiomyomas and 1 case was leiomyosarcoma. In the group of esophageal GISTs, 3 cases were male, and 2 cases were female. Their age ranged from 44-63 years (mean 52 ± 7.8 years). In the group of leiomyomas and leiomyosarcomas, 13 cases were male, and 11 cases were female. Their age was between 24-68 years (mean 55 ± 10.2 years). The symptoms of esophageal mesenchymal tumors are summarized in Table 1.

### Endoscopic and EUS characteristics

Endoscopically, GISTs showed submucosal protuberant lesions such as hemisphere, nodosity, strip or irregular shape, and had smooth surface, wide bases and the same color as its adjacent mucosa (Figures 1 and 2). The malignant lesions showed ulceration or hemorrhage, and had no clear boundaries with the normal tissue. Benign tumors varied from 0.5-3 cm in size. One malignant tumor

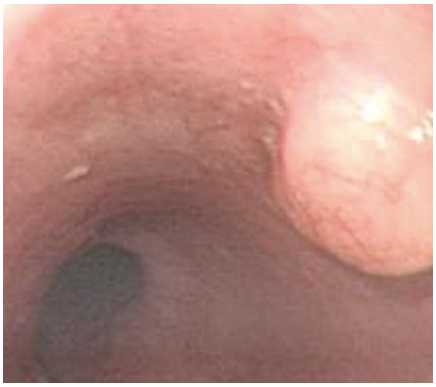

**Figure 2** Endoscopic image of leiomyomas.

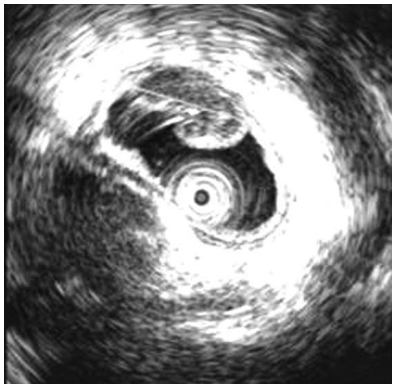

**Figure 3** EUS image of esophageal stromal tumors: originated from muscularis propria.

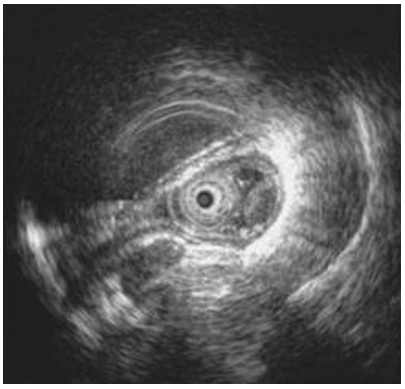

**Figure 4** EUS image of leiomyomas: originated from muscularis mucosa.

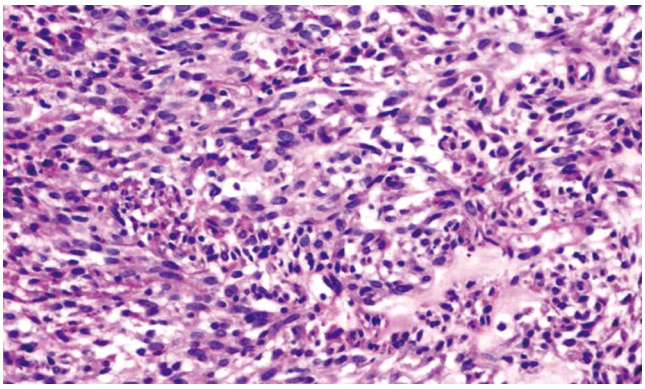

**Figure 5** Malignant esophageal stromal tumor: tumor cells were intensely stained, but there was no visible mitoschisis. (HE × 200).

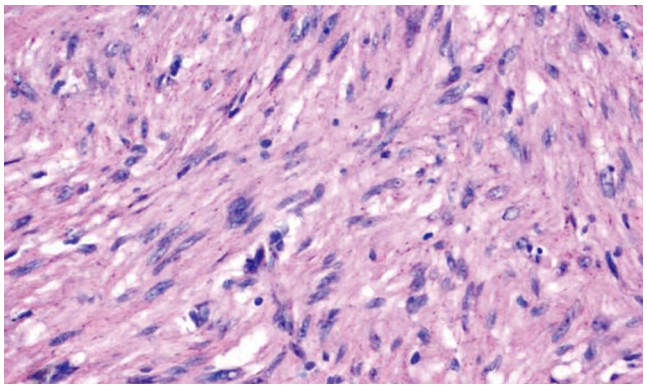

**Figure 6** Esophageal leiomyoma: cells were all spindle, with abundant eosinophilic cytoplasm (HE × 200).

was especially large, extending to the cardia and body of the stomach. LMs showed submucosal protuberant lesions such as polyps, hemisphere, pillar, dumb bell, with smooth surfaces. Tumors varied between 0.5-3 cm in size, and had clear borders. One leiomyosarcoma showed irregular nodosity. Its size was 3 cm × 4 cm with anabrotic surfaces.

On EUS, GISTs showed round, spindle-shaped or irregular low echo images originated from the muscularis propria or muscularis mucosa, from which internal echoes were homogeneous or heterogeneous. Two cases were originated from the muscularis mucosa and 3 cases from the muscularis propria (Figures 3 and 4). LMs also showed low echo images originated from the muscularis propria or muscularis mucosa and their internal echoes were homogeneous or heterogeneous. Eleven cases were originated from the muscularis mucosa and 12 cases were originated from the muscularis propria. Endoscopy and EUS could not differentiate esophageal GISTs from LMs because of their similar appearances.

### *Pathological characteristics*

Among 5 cases of GISTs, 4 cases were of spindle cell type, and one case was of epitheloid cell type. There was no mixture of cell types. The cells of GISTs were more intense than leiomyomas, and had a less eosinophilic cytoplasm. The spindle cells were arranged in braid, sarciniform, or cord-like and their nuclei were rod -like. The epitheloid cells were round, orbicular-ovate or polygon and their nuclei were conspicuous. According to the above mentioned criteria, there was 1 case of malignancy at the inferior segment of the esophagus, which size was uncertain, with hemorrhage and necrosis on its surface. Microscopically, the tumor cells were intense, but there was no visible mitoschisis (Figure 5).

Twenty three cases of LMs were composed of well-differentiated smooth muscle cells of spindle cell type and the cells were arranged as braid, sarciniform. The tumors were moderately cellular with abundant eosinophilic cytoplasm (Figure 6). According to the criteria, there was one leiomyosarcoma, which size was 3 cm × 4 cm, with ulceration and bleeding on its surface and without clear borders. Microscopically, there were abundant spindle cells with a few mitoschisis.

Among 29 cases of esophageal mesenchymal tumors, one case with malignancy (20%) was found in 5 cases of esophageal GISTs, and one case with malignancy (4.2%) was found in 24 cases of leiomyomas and leiomyosarcomas. Using Fisher's exact method, the differences of malignant lesions proportion were not significant between esophageal LMs and GISTs, 1/5 *vs* 1/24 ($P > 0.05$).

### *Immunohistochemical results*

Twenty nine cases of esophageal mesenchymal tumors

**Table 2 Expression of CD117 in 29 cases of esophageal mesenchymal tumors**

| Tumor type | *n* | Positive rate (%) |
|---|---|---|
| GISTs | 5 | 5 |
| LMs | 24 | 0 |
| | $P < 0.003$ | |

**Table 3 Expression of CD34 in 29 cases of esophageal mesenchymal tumors**

| Tumor type | *n* | Positive rate (%) |
|---|---|---|
| GISTs | 5 | 3 (60) |
| LMs | 24 | 0 |
| | $P < 0.003$ | |

**Table 4 Expression of SMA in 29 cases of esophageal mesenchymal tumors**

| Tumor type | *n* | Positive rate (%) |
|---|---|---|
| LMs | 24 | 24 (100) |
| GISTs | 5 | 2 (40) |
| | $P < 0.003$ | |

**Table 5 Expression of desmin in 29 cases of esophageal mesenchymal tumors**

| Tumor type | *n* | Positive rate (%) |
|---|---|---|
| LMs | 24 | 24 (100) |
| GISTs | 5 | 1 (20) |
| | $P < 0.003$ | |

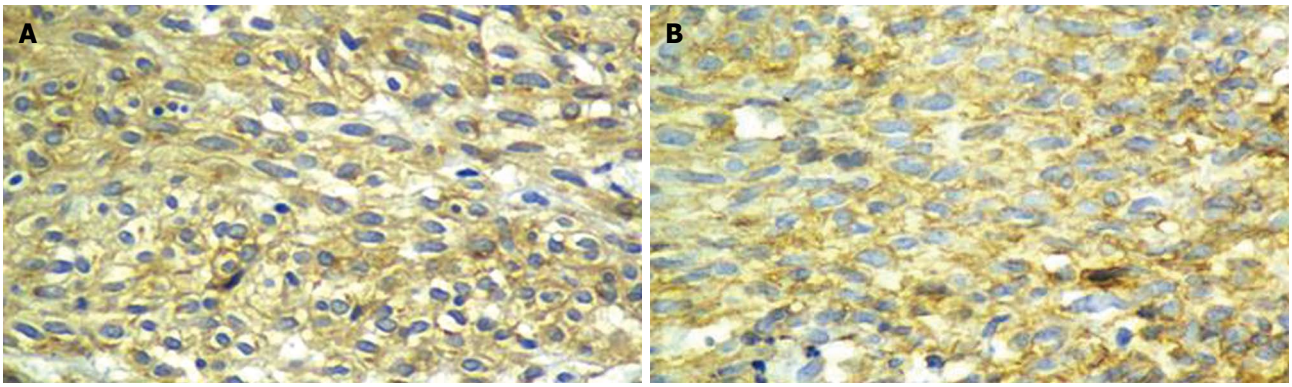


**Figure 7** Expression of CD117(× 200) and CD 34 (× 400) in malignant esophageal stromal tumor: showing yellow or brown granules in cell cytoplasm and (or) membrane. **A**: CD117; **B**: CD34.

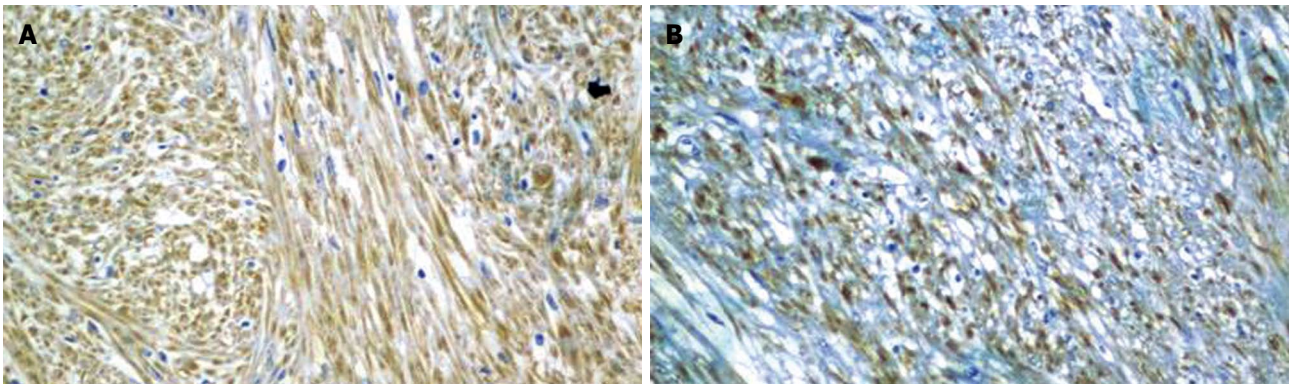


**Figure 8** Expression of SMA (**A**) and Desmin (**B**) in esophageal leiomyomas (× 200): showing yellow or brown granules in cell cytoplasm.

were all stained positive for CD117, CD34, SMA and desmin. The results are summarized in Table 2, Table 3, Table 4 and Table 5, Figures 7 and 8.

## DISCUSSION

Gastrointestinal mesenchymal tumors have long been classified as LMs, including leiomyoma and leiomyosarcoma. In 1983 Mazur and Clark introduced the term of gastrointestinal stromal tumors (GISTs). GISTs are a kind of potentially malignant tumor. Most scholars believe that the stomach is the predilective site of GISTs, next are the intestines, the colon and the rectum. And GISTs seldom occur in the esophagus[9,10].

Gouveia[11] reported that esophageal GISTs, though less in number, were also made up of fusiform cells, and their mitotic index was low. CD117 and CD34 were expressed, and the malignant degree was low. Among 57 cases of esophageal mesenchymal tumors, studied by Madalie[12], 14 cases of esophageal GISTs were found, and only 2 cases were malignant. Wang[13] reported that 9 cases of GISTs were found among 44 cases of esophageal mesenchymal tumors, and 3 cases were malignant. In our study, among 29 cases of esophageal mesenchymal tumors, 5 cases were demonstrated to be GISTs by endoscopy, pathology, and immunochemistry, and the other 24 cases were LMs. This result further proved that esophageal GISTs exist in the gastrointestinal tract, though they are fewer in number than esophageal LMs, accounting for only 20%[12-14].

Esophageal mesenchymal tumors mostly occur in people of middle and old age, especially over 50 years old, occasionally in children. In the current study, all the 5 cases were over 40 years old, and 3 of them were over 50 years old (the youngest one was 40 years old). The mean age was 52 years. Esophageal leiomyomas may occur at any age. In our group, age of patients with LMs was from 20 to 70 years, and males were slightly more than females. The clinical manifestations of esophageal mesenchymal tumors are closely correlated with the size, nature, and growth pattern of the tumor. In the earlier period, clinical symptoms are nonspecific. When the tumor volume becomes bigger grossly and grows intracavitarily, symptoms such as dysphagia, heart burn, and retrosternal pain may become obvious. Some patients may have upper gastrointestinal hemorrhage.

The appearance of esophageal GISTs and leiomyomas are similar under the endoscope. They are generally globular, hemispheroid, polypoid, with tubercular eminences. The surface of benign GIMTs is smooth, while there is ulceration or hemorrhage on the surface of malignant GIMTs. EUS can not only examine the wall of the esophagus, but can also estimate the topography of the extent, location of lesions, and their relation to the surrounding organs[15,16]. EUS can discriminate GIMTs from other protrusion lesions of the esophagus. Usually esophageal mesenchymal tumors show a low echo image. Though EUS can help doctors to make therapeutic decisions by surgery or by endoscopy, it cannot help doctors to judge the type of the GIMTs.

Esophageal GISTs originate from between the walls of the esophagus. They are a kind of proliferation of spindle cells or epithelioid cells. No matter where the tumor is originated, the cells of GISTs are more abundant than that of leiomyomas and have less eosinophilic cytoplasm. The tumor cells are interlaced，dispersed, or paliformly arranged. In our study, cell nests made up of spindle cells were found in three cases of esophageal GISTs. These cell nests can only be found in GISTs, but not in LMs. This result is coincident with that of Franquemont[17].

There is no definite criterium for differentiation between benign and malignant esophageal mesenchymal tumors. We determined the nature of tumors according to their infiltration, metastasis, volume, and nuclear mitotic figure. In the present study, one case of interstitialoma occurred at the inferior segment of the esophagus. Its diameter was more than 5 cm. There was ulceration and hemorrhage on the surface, but no obvious mitoschisis. This tumor can still be judged as malignant. Kimiyoshi[18] suggested a criterium for differentiation between benign and malignant GISTs: hemorrhage or necrosis, the diameter of the tumor > 5 cm, Ki-67 labeling index (LI) > 3%. If the tumor has any one of the items above, it is malignant. If none of the items above can be found, then it is benign. Kimiyoshi also found that cellulosity, nuclear atypia, and mitoschisis were not related to the nature of the tumor. This is different from the traditional diagnostic criteria. And further studies are needed. Leiomyosarcomas are not common, and its diagnostic criteria are not well studied. According to the criteria of WHO, there was only 1 case of leiomyosarcoma in the present study. The tumor occurred at the inferior segment of the esophagus. Intensive fusiform cells could be seen under the microscope. Mitoschisis could be seen accidently. The diagnosis was low potential malignant leiomyosarcoma. The incidence of esophageal leiomyosarcoma is low.

In our study, the difference between the ratio of malignant GISTs (1/5) and that of leiomyosarcoma (1/24) was insignificant. It showed that the biological behaviour of GISTs was related to the site of the tumor. Esophageal GISTs are not as malignant as those in the gastrointestine. It was also noted that 1 case of esophageal leiomyosarcoma and 1 case of esophageal interstitialoma both occurred in the inferior segment of the esophagus adjacent to the cardia. Whether the predilection site for malignant lobus intermedius tumor is the inferior segment of the esophagus is still to be studied.

In 1998, Kindblom *et al*[19] found that GISTs expressed CD117, which provided an effective means to study GISTs. CD117 is sensitive and specific. Studies reported that the sensitivity was 90%-100%[20,21]. In this study, all 5 cases of esophageal interstitialoma expressed CD117, while no case of leiomyoma expressed CD117. Both the sensitivity and specificity were 100%. This result is coincident with most overseas studies. However, not all GISTs expressed CD117. Debiec-Rychter found that in some of the malignant or recurrent cases of GISTs, CD117 was not expressed[22]. CD34 is a sensitive immunochemistry marker of GISTs. CD34 was expressed in 60%-70% cases of GISTs[23,24], but barely expressed in leiomyomas and myoschwannomas[25,26]. In our group the sensitivity of CD34 was 60%, and the specificity was 100%. Smooth muscle actin(SMA) is widespread and strong positive in smooth muscles, and also positive in GISTs. This shows that some GIST cells could differentiate into smooth muscles. Desmin is a key index for diagnosis and differential diagnosis of GIMTs, which is strongly expressed in smooth muscles, while barely expressed in GISTs. In this group, desmin was positive in all 24 cases of leiomyoma (leiomyosarcoma); only positive in 1 GIST. This is consistent with previous reports[27,28].

Our study provided evidence that all esophageal mesenchymal tumors had the same immunohistochemical features, and combined detection of CD117, CD34, SMA and desmin can help differentiate esophageal GISTs from LMs.

In summary, the present study demonstrates that

the traditional classification is not precise by combined analysis of the clinical, endoscopic, pathological and immunohistochemical features of esophageal mesenchymal tumors. Clinical findings, endoscopy and EUS can be helpful for diagnosis of esophageal mesenchymal tumors, but cannot determine the nature of tumors. Pathology and immunohistochemistry play an important role in their diagnosis and differential diagnosis.

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